Secondary Primary Lung Cancer After Esophageal Cancer: A Population-Based Study of 44,172 Patients

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Research

Keywords: esophageal cancer, lung cancer, secondary primary malignancy, overall survival, population-based study, multiple imputation

Posted Date: June 25th, 2020

DOI: https://doi.org/10.21203/rs.3.rs-37461/v1

Version of Record: A version of this preprint was published at Scandinavian Journal of Gastroenterology on November 2nd, 2021. See the published version at https://doi.org/10.1080/00365521.2021.1994639.

Abstract

Background: The present study aimed to assess the incidence, characteristics, and survival of secondary primary lung cancer after primary esophageal cancer (EC-LC).

Methods: The patients with esophageal cancer (EC) who developed SPLC and patients with first primary lung cancer (LC-1) were retrospectively reviewed in the Surveillance, Epidemiology, and End Results 18 registries covering 2000 to 2016. The risk of secondary primary lung cancer using standardized incidence ratio (SIR) was calculated among patients with EC. Overall survival and characteristics were compared between patients with EC-LC and patients with LC-1.

Results: In comparison with the general population, the patients with EC had a higher risk for developing secondary primary lung cancer (SIR =1.86, 95% confidence interval (CI): 1.69-2.05). There was a significant difference with regard to the year of diagnosis, sex, grade and stage between the secondary primary lung squamous carcinoma after EC (EC-LUSC) and first primary lung squamous carcinoma (LUSC-1) patients. A statistically significant difference with respect to race, sex, age, year, grade and stage was found between the secondary primary lung adenocarcinoma after EC (EC-LUAD) and first primary lung adenocarcinoma (LUAD-1) patients. A history of EC was found to be an independent risk factor of death for lung squamous carcinoma and lung adenocarcinoma patients in localized stage based on multivariate Cox regression analysis, propensity score-matching analysis and multiple imputation.

Conclusion: There is a significantly increased risk of secondary primary lung cancer in EC survivors and a history of EC adversely affects overall survival in individuals who subsequently develop localized EC-LUSC and EC-LUAD. Clinicians should moderately strengthen lung tissue protection during the management of EC patients.

Background

Esophageal cancer (EC) is the sixth most common cause of cancer-related death, leading to approximately four hundred thousand deaths per year[1]. Although esophageal cancer incidence rates in U.S. have tended to decrease[2-3], the incidence rates of secondary primary malignancy (SPM) after EC have tended to increase because of increasing numbers of long-term cancer survivors[4]. Previous several population-based studies have demonstrated that patients with EC are at increased risk of developing SPM, with standardized incidence ratios (SIRs) range from 1.15 to 3.53 in comparison with the general population[5-7]. Lung cancer (LC) is one of the most frequently occurring SPM after an EC. There have been several studies describing an increased incidence of secondary primary lung cancer (SPLC) in the EC population, which may be explained by the concept of “field cancerization”[5-10]. Notwithstanding several reports have discussed the risk of SPMs, including SPLC, most of these exclusively focused on the frequency of and risk factors of SPMs, rather than focusing on the subsequent survival. As far as we know, no study has specifically examined the overall survival (OS) after a diagnosis of LC in patients with a history of EC. The object of the research using data from the Surveillance, Epidemiology, and End

Results (SEER) Program was to examine the incidence and clinical and pathologic characteristics of patients with SPLC after EC and evaluate the effect of a history of EC on OS in patients with SPLC after EC (EC-LC) in comparison with those with LC-1.

Methods

Risk for EC-LC

Patients were identified from SEER 18 registries covering 2000 to 2016. A total of 424 lung cancers occurring greater than or equal to 2 months after EC were identified. The variables examined were sex, race, latency, age at EC diagnosis and year of EC diagnosis. Of these variables, race was evaluated in three categories (white, black, and others). Latency was categorized into four groups (2-11 months, 12-59 months, 60-119 months and ≥120 months). Age was assessed in four categories (<50, 50-59, 60-69, ≥70). Year was categorized into three groups (2000-2004, 2005-2009 and 2010-2016). The expected numbers of second malignancy were calculated for a reference population of identical race and/or ethnicity, attained age, sex, as well as time period. The risk of SPLC was defined as the SIR, which measured the relative strength of association between two malignancies. The SIR was calculated as the ratio of observed to expected second malignancy. Two-sided 95% confidence intervals (CIs) as well as P-values for SIR were based on Poisson exact methods[11], and SIR values were considered significantly elevated at $P < 0.05$. The criteria of nonoverlapping 95% CIs were utilized to show a statistically significant difference when compared SIRs in different subgroups. The above analysis was performed by using SEER*Stat release 8.3.6.

Characteristics and prognosis of EC-LC and LC-1

A total of 410 EC survivors with ≥1 subsequent lung malignancies were identified. Some of survivors (396 EC patients) developed one primary lung malignancy, and others (14 EC patients) developed two primary lung malignancies. For these patients which developed two primary lung malignancies, their first subsequent lung malignancies were enrolled in the study and the remaining subsequent lung malignancies were eliminated. Finally, we enrolled 410 subsequent lung malignancies in our study. For comparison, three pathological types of LC-1 inculding 108582 first primary lung squamous carcinomas (LUSC-1), 204723 first primary lung adenocarcinomas (LUAD-1), and 66759 first primary small cell lung carcinomas (SCLC-1) were identified in the same SEER registries. Patient and tumor characteristics were compared using chi-square tests with theoretical frequency great than or equal to five. The data were analyzed by continuity correction when theoretical frequency less than five but at least one (less than or equal to 20% cell). Fisher's exact test was utilized as for the rest of it. Standardized adjusted residuals (SARs) for the cell percentage of each subcategory were calculated to determine which cell differences resulted in the statistically significant results. Subcategories had significant difference to the overall percentages when SAR > 1.96 for the percentages of corresponding subcategories. The overall survival (OS) time was calculated from the date of LC diagnosis to the date of last follow-up or death from any

cause. We used the Kaplan-Meier (KM) method and log rank test to compare the OS of EC-LC and LC-1 patients, according to SEER stage (localized, regional, and distant stage) to group. Multivariable analysis was performed by using a Cox regression model to assess the effect on prognosis of a history of EC after adjusting for sex, age at LC diagnosis, race, year of LC diagnosis, LC grade and surgery for LC, according to SEER stage to group. In order to reduce the error generating by misdiagnosis of synchronous primary cancers as SPLC and misclassification of metastatic disease as SPLC, sensitivity analyses were performed by omitting cases with <one-year and <two-year latency to SPLC diagnosis. We analyzed information for all complete cases and applied multiple imputation[12] (5 repetitions) for all cases. The multivariable analysis was performed after using multiple imputation. In addition, propensity score-matching (PSM), subsequently KM analysis and multivariate analysis by Cox regression were conducted to re-assess the effect on prognosis of a history of EC. One-to-four nearest neighbor PSM without replacement was conducted with a caliper width of 0.05 prior to survival analysis. All tests were two-sided. A $P < 0.05$ was defined as statistically significant. Chi-square tests, continuity correction, Fisher's exact test, and SAR calculation were performed by SPSS release 25.0. Multiple imputation, KM analysis, Cox regression analysis and PSM were performed by R release 3.6.1.

Results

SIRs for EC

A total of 44172 patients were diagnosed with EC in the SEER 18 Program database between 2000 and 2016. The characteristics of these patients with EC are shown in Figure 1. Of these cases with EC who were followed for a total of 85011.69 person-years at risk, 424 developed a SPLC. SIR was utilized to evaluate the incidence of SPLC. In comparison with the general population, higher rates of SPLC occurred among patients with EC (SIR = 1.86, 95% CI:1.69-2.05). The risk of developing SPLC was statistically significantly elevated in all subgroups when grouped cases with SPLC according to different standards.

Compared with male EC patients, female had the higher risk for a SPLC, with statistical significance. The risk of developing a SPLC was significantly lower in white patients (SIR 1.74, 95% CI: 1.56-1.93) than black patients (SIR 3.02, 95% CI: 2.31-3.87). For an analysis by latency, the risk (SIR) for a SPLC increased progressively with advancing latency, but with no significant difference. The maximum risk (SIR) was seen for EC patients younger than 50 years (SIR 4.97, 95% CI: 2.78-8.2), which was significantly higher than the risk for patients aged 60-69 years (SIR 2.11, 95% CI: 1.81-2.44) and older than 70 years (SIR 1.29, 95% CI: 1.08-1.51). We noted that there was no significantly increase on the risk (SIR) developing a SPLC during study periods by patient’s year of EC diagnosis.

Patient and Tumor Characteristics

Table 1 outlines the patient and EC characteristics for patients with SPLC at time of diagnosis of EC. Among the SPLC histological subtype groups, the distribution of sex, race, latency, age at EC diagnosis,

year of EC diagnosis, stage of EC, site of EC and surgery for EC was similar. The SPLC histological subtypes were associated with histological subtype (P = 0.004) and grade (P = 0.005) of EC (Table 1 and Supplementary Table 1). Patients with secondary primary lung squamous carcinoma after EC (EC-LUSC) were more likely to have a history of esophageal squamous carcinoma (ESC) as 54.0% of them had a history of ESC (SAR = 3.1). Similarly, patients with secondary primary lung adenocarcinoma after EC (EC-LUAD) were more likely to have a history of esophageal adenocarcinoma (EAD) as 58.7% of them had a history of EAD (SAR = 2.6). Individuals with EC-LUAD tended to have a lower grade of EC (53.8%, SAR = 2.8), while individuals with EC-LUSC tended to have a higher grade of EC (68.6%, SAR = 2.9).

Table 2 outlines the baseline characteristics of EC-LUSC and LUSC-1 patients. There was a nonsignificant difference with regard to race, age at lung squamous carcinoma (LUSC) diagnosis and surgery for LUSC between the EC-LUSC and LUSC-1 patients. There was a significantly different distribution of year of LUSC diagnosis (P < 0.001) (Table 2 and Supplementary Table 2). SARs demonstrated that EC-LUSC were more prevalent than LUSC-1 in individuals diagnosed from 2010 to 2016. In addition, sex differed significantly depending on the type of LUSC (P = 0.010), with patients with EC-LUSC more likely to be male. We found a statistically significant difference with respect to grade of disease between the EC-LUSC and LUSC-1 patients (P = 0.008). In comparison with LUSC-1 patients, EC-LUSC patients were more likely to be diagnosed at the well differentiated grade (8.6%, SAR = 2.8). Conversely, LUSC-1 patients tended to be diagnosed at the poorly differentiated and undifferentiated grade (54.4%, SAR = 2.2). There was a significant relationship with regard to stage between the EC-LUSC and LUSC-1 patients (P < 0.001). Patients with EC-LUSC tended to be diagnosed at an earlier stage compared with patients with LUSC.

Table 2 outlines the baseline characteristics of EC-LUAD and LUAD-1 patients. There were no significant differences with regard to surgery for lung adenocarcinoma (LUAD) between the EC-LUAD and LUAD-1 patients, which were similar to the results in the LUSC cohorts (including EC-LUSC and LUSC-1 patients). We found a statistically significant difference with respect to sex, race, age at LUAD diagnosis, year of LUAD diagnosis, stage of LUAD, grade of LUAD, and surgery for LUAD between the EC-LUAD and LUAD-1 patients (Table 2 and Supplementary Table 3). Patients from other races in the EC-LUAD group were more prevalent than those in the LUAD-1 group. Patients with LUAD-1 were more likely to be diagnosed at a younger age than patients with EC-LUAD. Compared with LUAD-1, EC-LUAD were more prevalent in individuals diagnosed in recent years (2010 to 2016). There was a significantly different distribution of sex, with individuals with EC-LUAD tending to be male (P < 0.001). However, the male-female ratio approximately turned out equal for individuals with LUAD-1. In addition, we found that EC-LUAD was significantly more likely to be of lower grade compared with LUAD-1 (P = 0.028). SARs demonstrated that EC-LUAD patients with grade I (well differentiated grade) were more prevalent than LUAD-1 patients with grade I, while EC-LUAD patients with grade III/IV (poorly differentiated and undifferentiated grade) were less prevalent than LUAD-1 patients with grade III/IV. Moreover, The stage of LUAD differed significantly between the EC-LUAD and LUAD patients (P < 0.001). SARs showed that the prevalence of EC-LUAD patients with localized stage was higher, while that with distant stage was lower. Supplementary Table 4 outlines the baseline characteristics of secondary primary small cell lung cancer after EC (EC-SCLC) and the first primary small cell lung cancer (SCLC-1) patients. We did not find a statistically significant

difference with regard to race, age, sex, grade and stage between the SCLC-1 and EC-SCLC patients. However, there was a significant difference with respect to year of diagnosis (P = 0.007) (Supplementary Table 4 and Supplementary Table 5). Compared with SCLC-1 patients, EC-SCLC patients were more prevalent in individuals diagnosed earlier this decade (2000 to 2004).

Survival

Supplementary Table 6 shows the comparisons of crude survival statistics between EC-LC and LC-1 patients. The leading cause of death among SPLC patients regardless of pathologic types was LC. In comparison with individuals with EC-LUSC, those with LUSC-1 experienced relatively fewer deaths from other cancers, with similar results in patients with other LC pathologic types.

KM methods were used to compute the survival analyses for LUSC and LUAD among survivors of EC and individuals with LC-1 (we did not conduct the survival analyse for SCLC because of sample limitations). A comparison of the unadjusted OS between LUSC-1 and EC-LUSC patients is shown in Table 3. For individuals with LUSC of localized, regional, and distant stage, the median OS of individuals with LUSC-1 was 40 months, 18 months and 7 months, while the median OS of individuals with EC-LUSC was 20 months, 14 months and 7 months, respectively. In comparison with LUSC-1 patients in localized stage, the survival rate of EC-LUSC patients in localized stage was significantly lower (P < 0.001). However, these differences in other stages were not found to be statistically significant (regional, P = 0.140; distant, P = 0.229). Six-month, one-year, two-year and three-year survival rates for EC-LUSC patients in localized stage were 81.0%, 55.3%, 46.7% and 29.5%, respectively. And six-month, one-year, two-year, three-year, five-year and ten-year survival rates for LUSC-1 patients in localized stage were 89.7%, 79.5%, 63.9%, 53.3%, 40.0% and 19.7%, respectively. A comparison of the unadjusted OS between LUAD-1 and EC-LUAD patients is shown in Table 3. For individuals with LUAD of localized, regional, and distant stage, the median OS of individuals with LUAD-1 was 81 months, 33 months and 8 months, while the median OS of individuals with EC-LUAD was 30 months, 34 months and 7 months, respectively. In comparison with the survival rate of LUAD-1 patients in localized stage, the one of EC-LUAD patients in localized stage was significantly lower (P < 0.001).

Then multivariable analysis was performed applying a Cox regression modeling to assess the effect of a history of EC in patients with localized stage. We applied this model adjusted for sex, race, age at LC diagnosis, year of LC diagnosis, grade of LC, and surgery for LC. For LUSC in localized stage, results are presented in Table 4 for the 19531 individuals with complete information on all variables as well as subsequently using multiple imputation method for all 24760 individuals. For LUAD in localized stage, results are presented in Table 4 for the 36100 individuals with complete information on all variables as well as subsequently using multiple imputation method for all 44615 individuals. A history of EC was found to be a poor-prognostic factor for LUSC and LUAD patients in localized stage. For LUSC in localized stage, the hazard ratio (HR) for a history of EC was 2.49 (95% CI, 1.75-3.54) in the analysis of the 19531 individuals with complete information and was 1.91 (95% CI, 1.48-3.05) in the analysis of the

24760 individuals by using multiple imputation method. For LUAD in localized stage, the HR for a history of EC was 2.63 (95% CI, 1.71-4.03) in the analysis of the 36100 individuals with complete information and was 2.13 (95% CI, 1.48-3.05) in the analysis of the 44615 individuals by using multiple imputation method. For purpose of reducing the error generating by misdiagnosis of synchronous primary cancers as SPLC and misclassification of metastatic disease as SPLC, we omitted cases with <one-year and <two-year latency to SPLC diagnosis. Whether in LUSC in localized stage or in LUAD in localized stage, results after omitting patients with <one-year and <two-year latency were not changed obviously.

Propensity score-matching analysis was performed to re-evaluate the effect of a history of EC in patients with localized stage. For LUAC in localized stage, a total of 205 patients (41 EC-LUSC patients and 164 LUSC-1 patients) were included after propensity matching. Subsequent KM analysis (Figure 2) and multivariate analysis redemonstrated that a history of EC was a poor-prognostic factor for LUSC (median OS, 20 versus 56 months; HR, 2.37 (95% CI, 1.56-3.60), P < 0.001). A similar result was found for LUAD in localized stage. A total of 192 patients (39 EC-LUAD patients and 153 LUAD-1 patients) were included after propensity matching. Subsequent analyses (Figure 2) showed again that a history of EC correlated with worse prognosis for localized stage LUAD (median OS, 29 versus 110 months; HR, 3.24 (95% CI, 1.84-5.69), P = 0.012).

Discussion

Increased Risk of a SPLC After EC

In this study, we found a statistically significant increase in SPLC risk in all EC survivors in comparison with the incidence rates of general population, with similar results having been reported in some studies[5-8,10], which focused more on the overall second primary cancer risk rather than SPLC risk. In this large population-based study, the data of EC-LC patients were reviewed in more detail and SIRs were assessed for different patient groups with regard to race, latency, age, year of diagnosis and sex. DeSantis et al reported that LC incidence rates are 15% higher in black men than in white men and the opposite was true for women[13]. And they pressed further, and found that higher rates of LC among black men were limited to NSCLC. The majority of EC-SPLC patients in our study were men (73.6%) and NSCLC patients (93.4%). These results maybe account for this phenomenon that the risk (SIR) for a SPLC was higher in black individuals than white individuals, though reasons for this phenomenon were unknown. In this study we found that the risk of developing a SPLC varied between the sexes, with females having the higher risk for a SPLC. According to a major international study[14], male was especially at mortality risk of esophagus cancer, with two or three times the overall mortality rate of female worldwide. In consideration of the better prognosis in female, female with esophagus cancer might be more likely to survive its initial primary cancer (EC) and continue to experience development of a second primary cancer. It was a similar result to a reported 2018 research that claimed that female with initial primary lung cancer was at lower risk for development of a SPLC[15]. The SPLC risk gradually decreased with age at EC diagnosis, which could be most likely caused by the same reason[16-17]. The fact that the total cancer incidence increased when the age of the patients increased might also interpret

the age-related changes in SIR. In our study, we found that the SPLC risk increased progressively with advancing latency, though with no significant difference. There was a 134% increased risk of developing a SPLC after a latency of >10 years compared to the general population, suggesting a reasonable long-term follow-up protocol should be designed for individuals with EC.

Patient and Tumor Characteristics

We observed that the SPLC histological subtypes were associated with histological subtypes of EC. Adjusted standardized residuals demonstrated that the proportion of the EC-LUSC patients which had a history of ESC was significantly higher than that which had a history of other EC histological subtypes. Similarly, the proportion of the EC-LUAD patients which had a history of EAD was significantly higher than that which had a history of other EC histological subtypes. The high frequency of multiple primary carcinoma in patients with lung and upper aerodigestive tract cancers might be explained by the phenomenon of 'field cancerization'[9,18-20]. One explanation of the concordant histology between EC and subsequent LC might be exposure of the epithelium of lung and upper aerodigestive tract to some of the same carcinogens. Besides, Several master development regulators were significantly altered in squamous cell carcinomas across multiple organ sites, which were drivers of carcinogenesis[21]. These altered regulators in EC might be associated with development of second primary malignancy which was similar to EC in histological subtypes. We also found that the SPLC histological subtypes might be associated with grades of EC. However, around a quarter of EC individuals (23.7%) were unknown grade, therefore the result might be biased and interpreted with the greatest care. We observed that patients with EC-LUSC and EC-LUAD were more often diagnosed in recent years (2010 to 2016) compared to patients with LC-1.These results might be attributed to the improvement of diagnostic technique over time and shorter follow-up intervals of EC patients. In fact, some researches confirmed that cancer survivors received more frequent screening for various subsequent primary cancers than patients without a history of cancer[22-24]. The fact that cancer survivors might receive better surveillance for new cancers also explained why individuals with previous EC tended to diagnosed at an earlier stage compared with LC-1 individuals in this study, which was consistent with previous study[25]. Though we found that patients with EC-LUAC and EC-LUAD were more likely to be diagnosed at a lower grade, this result might be biased because of a large number of patients with unknown grade. In addition, patients with EC-LUSC and EC-LUAD were more likely to be male than patients with LUSC-1 and EC-LUAD respectively, which was perhaps partially reflective of the different male to female ratio between the EC and LC patients in North America. According to a status report on the global burden of cancer in 2018, there was a 4.7-fold variation in esophagus cancer rates by gender in North America, whereas the variation in lung cancer was only 1.3-fold [8], which verified the validity of the above hypothesis.

Overall Survival

To the best of our knowledge, this was the first population-based study to specifically examined overall survival of patients with EC-LC. The attention had been paid to investigating the effect of second primary cancer on survival outcomes of patients with EC. Lee et al found that esophageal cancer patients with synchronous second primary cancers had poor survival than that those without them[26]. Kudou et al found a similar result in esophageal cancer patients with metachronous second primary cancers[27]. Different from the past research angles of view that focused on survival outcomes in EC patients with second primary cancer compared with those with first primary EC, The research focused on patients survival outcomes with SPLC, one of the most common second primary cancer of esophagus cancer, by comparing the patients with LC-1. Base on the results of the Kaplan-Meier analysis, we found that in comparison with LUSC-1 patients in localized stage, the survival rate of EC-LUSC patients in localized stage was significantly lower. And similar results were shown in EC-LUAD patients. Subsequent multivariable Cox analyses demonstrated that a history of EC was an independent risk factor of death for LUSC and LUAD patients in localized stage. The survival outcomes of second primary non-small-cell lung cancer individuals had been reported for other primary sites. The survival outcomes of those patients varied with the difference of first primary sites. Budnik et al indicated that a history of head and neck cancer had a detrimental impact on overall survival in survivors who subsequently develop non-small-cell lung cancer regardless of stage[28]. However, US researchers found that a history of breast cancer did not appear to adversely affect overall survival after non-small-cell lung cancer[29]. This study first showed that patients with localized EC-LUSC and EC-LUAD had the inferior survival compared with patients with de novo localized LUSC and LUAD respectively, which were further confirmed with propensity score-matching analyses. We speculate that the inferior overall survival of patients with localized EC-LUSC and EC-LUAD might have been due to more aggressive treatment and host factors inherent to the development of esophagus cancer. Besides, in this study we found that a certain percentage of patients with localized EC-LUSC and EC-LUAD died of first primary cancer (EC). Different survival outcomes in different disease sites might be due to the different magnitude of excess mortality from the antecedent malignancy.

Missing data represented one of the inevitable features of population-based databases including SEER database[30]. Complete case analysis might introduce considerable bias. Therefore we used the multiple imputation approach to handle missing data to reduce the effect of the bias. Subsequent multivariate analyses after applying multiple imputation still indicated that a history of EC was an independent risk factor for poor prognosis in the patients with localized LUSC and LUAD, which were consistent with complete case analyses. Besides, in order to minimizing the potential effects of misclassification of metastatic disease as SPLC and misdiagnosis of synchronous primary cancers as SPLC, cases with <one-year and <two-year latency to SPLC diagnosis were omitted and subsequent multivariate Cox regression analyses were performed. There were no obvious changes in order of magnitude to the HR for localized LUSC and LUAD before and after omitting cases. Sensitivity analyses included multiple imputation of missing values and restriction to cases showed that the results of worse survival for patients with localized EC-LUSC and EC-LUAD compared to those with a de novo localized LUSC and LUAD respectively were stable.

Limitations of Retrospective Data

Regardless of the fact that this population-based study has the advantage of containing a large number of EC survivors who develop SPLC, there are some limitations with regard to retrospective population-based study. First, we left out of consideration other factors potentially having an effect on SPLC risk and survival after SPLC. Some treatment information such as whether or not be treated with radiation and chemotherapy and details of treatment are largely unknown and some important individual patient data such as alcohol status, smoking status, presence of concurrent disease are not provided in the SEER registry. Furthermore, we cannot do a bit deeper analysis for EC-SCLC due to sample limitations and small sample sizes of EC-SCLC may make some research results lose statistical power. Larger studies are needed to evaluate the impact of EC history on the prognosis of patients with EC-SCLC in the future.

Conclusions

The present study provides a broad overview on SPLC after EC, including clinical and pathologic characteristics as well as prognosis. There is a significantly increased risk of SPLC in EC survivors and a history of EC adversely affects OS in individuals who subsequently develop localized EC-LUSC and EC-LUAD. The clinical significances comprise moderately strengthening lung tissue protection and frequent surveillance of the lung during the management of EC patients. Besides, in consideration of the poorer prognosis of localized stage EC-LUSC and EC-LUAD patients after EC, more aggressive treatment is necessary. Larger studies, especially in EC-SCLC and non-localized EC-LUSC and EC-LUAD patients is needed.

List Of Abbreviations

secondary primary lung cancer after primary esophageal cancer: EC-LC; esophageal cancer: EC; first primary lung cancer: LC-1; standardized incidence ratio(s): SIR(s); confidence interval(s): CI(s); secondary primary lung squamous carcinoma after EC: EC-LUSC; first primary lung squamous carcinoma: LUSC-1; secondary primary lung adenocarcinoma after EC: EC-LUAD; first primary lung adenocarcinoma: LUAD-1; first primary small cell lung carcinomas: SCLC-1; secondary primary small cell lung cancer after EC: EC-SCLC; secondary primary malignancy: SPM; Lung cancer: LC; secondary primary lung cancer: SPLC; overall survival: OS; Surveillance, Epidemiology, and End Results: SEER; secondary primary lung cancer after esophageal cancer: EC-LC; Standardized adjusted residual(s): SAR(s); Kaplan-Meier: KM; propensity score-matching: PSM; esophageal adenocarcinoma: EAD; hazard ratio: HR.

Declarations

Ethics approval and consent to participate:

The Second Affiliated Hospital of Nantong University institutional review board exempted this study from review because it uses deidentified publicly available data.

Consent for publication:

All authors agree to submit the article for publication.

Availability of data and material:

All data generated or analyzed during this study are included in this published article and its supplementary information files.

Competing interests:

The authors declare that they have no competing interests.

Funding:

This work was supported by Scientific Research Foundation of Nantong Health Committe (grant MB2019004) and Special Project of Clinical Medicine of Nantong University (grants 2019JY002 and 2019JQ006).

Authors' contributions:

Yadong Gao and Junbo Qian contributed to the conception of the study. Yadong Gao, Jianwei Qiu, Liugen Gu, Yanmei Yang Haifeng Kang, Yong Zhan, Shenglai Zhang, and Yan Zhang contributed significantly to analysis and manuscript preparation. Yadong Gao performed the data analyses and wrote the manuscript. Junbo Qian and Jianwei Qiu helped perform the analysis with constructive discussions.

Acknowledgements:

We want to thank one of Yadong Gao's best friends Shuai Xia, a software engineer for Baidu, for his assistance in data processing. Yadong Gao want to express his gratitude to Alan Tam and Leslie Cheung, two representative figures of the popular music circles in Hong Kong, whose music have given him powerful emotional support over the past years. Besides, Yadong Gao especially want to express his gratitude to Danfeng Li, the girl who he has had a crush on for 12 years. Anyway, Gao do not regret having loved the girl.

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Tables

Table 1 Patient and Tumor Characteristics at the Time of Esophagus Cancer Diagnosis

Characteristic	EC-LC	EC-LUSC	EC-LUAD	EC-SCLC	EC-other LCs	P valuea
Total	410 (100)	139 (100)	138 (100)	27 (100)	106 (100)	
Sex						0.762
Male	303 (73.9)	103 (74.1)	105 (76.1)	18 (66.7)	77 (72.6)	
Female	107 (26.1)	36 (25.9)	33 (23.9)	9 (33.3)	29 (27.4)	
Race						0.433c
White	335 (81.7)	110 (79.1)	114 (82.6)	25 (92.6)	86 (86.6)	
Non-Whiteb	75 (18.3)	29 (20.9)	24 (17.4)	2 (7.4)	20 (18.9)	
Latency						0.08
2-11 months	101 (24.6)	24 (17.3)	46 (33.3)	6 (22.2)	25 (23.6)	
12-59 months	190 (46.3)	72 (51.8)	52 (37.7)	13 (48.1)	53 (50.0)	
≥60 months	119 (29.0)	43 (30.9)	40 (29.0)	8 (29.6)	28 (26.4)	
Age at EC diagnosis						
<60	97 (23.7)	33 (23.7)	36 (26.1)	4 (14.8)	24 (22.6)	0.352
60-69	174 (42.4)	54 (59.0)	64 (46.4)	15 (55.6)	41 (38.7)	
≥70	139 (33.9)	52 (47.1)	38 (27.5)	8 (29.6)	41 (38.7)	
Year of EC diagnosis						0.768
2000-2004	146 (35.6)	52 (37.4)	43 (31.2)	11 (40.7)	40 (37.7)	
2005-2009	142 (34.6)	48 (34.5)	47 (34.1)	10 (37.0)	37 (34.9)	
2010-2016	122 (29.8)	39 (28.1)	48 (34.8)	69 (22.2)	29 (27.4)	
Stage of ECd						0.932

Localized	164 (40.0)	58 (41.7)	54 (39.1)	12 (44.4)	40 (37.7)	
Regional/Distant	206 (50.2)	67 (48.2)	71 (51.4)	14 (51.9)	54 (50.9)	
Unknown	40 (9.8)	14 (10.1)	13 (9.4)	1 (3.7)	12 (11.3)	
Histological subtypes of EC						0.004c
Squamous cell carcinoma	178 (43.4)	75 (54.0)	42 (30.4)	12 (44.4)	49 (46.2)	
Adenocarcinoma	203 (49.5)	59 (42.4)	81 (58.7)	14 (51.9)	49 (46.2)	
Others	29 (7.1)	5 (3.6)	15 (10.9)	1 (3.7)	8 (7.5)	
Grade of ECd						0.005
Well and moderately differentiated	179 (43.7)	72 (51.8)	49 (35.5)	16 (59.3)	42 (39.6)	
Poorly differentiated and undifferentiated	134 (32.7)	33 (23.7)	57 (41.3)	7 (25.9)	37 (34.9)	
Unknown	97 (23.7)	34 (24.5)	32 (23.4)	4 (14.8)	27 (25.5)	
Site of ECd						0.096c
Upper third of esophagus	28 (6.8)	15 (10.8)	4 (2.9)	3 (11.1)	6 (5.7)	
Middle third of esophagus	80 (19.5)	27 (19.4)	30 (31.7)	6 (22.2)	17 (16.0)	
Lower third of esophagus	227 (55.4)	66 (47.5)	84 (60.9)	15 (55.6)	62 (58.5)	
Unknown	75 (18.3)	31 (22.3)	20 (14.5)	3 (11.1)	21 (19.8)	
Surgeryd						0.304
Yes	199 (48.5)	70 (50.4)	73 (52.9)	12 (44.4)	44 (41.5)	
No	208 (50.7)	68 (48.9)	64 (46.4)	14 (51.9)	62 (58.5)	
Unknown	3 (0.7)	1 (0.7)	1 (0.7)	1 (3.7)	0	

Data were presented as n (%) except where otherwise noted

Abbreviations: EC, esophagus cancer; EC-LC, secondary primary lung cancer after EC; EC-LUSC, secondary primary lung squamous carcinoma after EC; EC-LUAD, secondary primary lung

adenocarcinoma after EC; EC-SCLC, secondary primary small cell lung cancer after EC; EC-other LCs, other secondary primary lung cancers after EC.

[a]P value from Chi-square test except where otherwise noted.

[b]Including Balck, Asian, Native American and Alaska Native/Pacific Islander.

[c]P value from Fisher's exact test.

[d]Unknown variables were omitted from Chi-square test and Fisher's exact test.

Table 2 Patient and Tumor Characteristics at the Time of LUSC and LUAD Diagnosis

	LUSC			LUAD		
	EC-LUSC	LUSC-1	P value[a]	EC-LUAD	LUAD-1	P value[a]
Total	139 (100)	108582(100)		138 (100)	204723 (100)	
Sex			0.010			<0.001
Male	103 (74.1)	68991 (63.6)		105 (76.1)	97813 (47.8)	
Female	36 (25.9)	39591 (36.5)		33 (23.9)	106910 (52.2)	
Race			0.323			0.011
White	110 (79.1)	89845 (82.7)		114 (82.6)	162489 (79.4)	
Black	23 (16.5)	13408 (12.3)		21 (15.2)	23340 (11.4)	
Others[b]	6 (4.3)	5191 (4.8)		3 (2.2)	18475 (9.0)	
Unknown[c]	0	138 (0.1)		0	419 (0.2)	
Age at LC diagnosis			0.209			<0.001
<60	17 (12.2)	19045 (17.5)		18 (13.0)	53219 (26.0)	
60-69	44 (31.7)	34793 (32.0)		62 (44.9)	63423 (31.0)	
≥70	78 (56.1)	54744 (50.4)		58 (42.0)	88081 (43.0)	
Year of LC diagnosis			< 0.001			<0.001
2000-2004	15 (10.8)	31150 (28.7)		9 (6.5)	51951 (25.4)	
2005-2009	35 (25.2)	31153 (28.7)		32 (23.2)	56646 (27.7)	
2010-2016	89 (64.0)	46279 (42.6)		97 (70.3)	96126 (47.0)	
Stage of LC			< 0.001			<0.001

Localized	58 (41.7)	24702 (22.7)		56 (40.6)	44559 (21.8)	
Regional	32 (23.0)	37851 (22.8)		32 (31.5)	46705 (22.8)	
Distant	42 (30.2)	42561 (39.2)		43 (31.2)	108603 (53.0)	
Unknown[c]	7 (5.0)	3468 (3.2)		7 (5.1)	4856 (2.4)	
Grade of LC			0.008d			0.028
Well differentiated	8 (5.8)	2427 (2.2)		21 (15.2)	19309 (9.4)	
Moderately differentiated	45 (32.4)	30218 (27.8)		36 (26.1)	46063 (22.5)	
Poorly differentiated and undifferentiated	40 (28.8)	38970 (35.9)		27 (19.6)	52808 (25.8)	
Unknown[c]	46 (33.1)	36967 (34.0)		54 (39.1)	86543 (42.3)	
Surgery for LC			0.265			0.063
Yes	45 (32.4)	32414 (29.9)		57 (41.3)	70390 (34.4)	
No	85 (61.2)	75168 (69.2)		78 (56.5)	133067 (65.0)	
Unknown[c]	9 (6.5)	10000 (0.9)		3 (2.2)	1266 (0.6)	

Data were presented as n (%) except where otherwise noted

Abbreviations: EC, esophagus cancer; LC, lung cancer; LUSC, lung squamous carcinoma; EC-LUSC, secondary primary LUSC after EC; LUSC-1, first primary LUSC; LUAD, lung squamous carcinoma; EC-LUAD, secondary primary LUAD after EC; LUAD-1, first primary LUAD

[a]P value from Chi-square test except where otherwise noted.

[b]Including Asian, Native American and Alaska Native/Pacific Islander.

[c]Unknown variables were omitted from Chi-square test and Fisher's exact test.

[d]P value from Fisher's exact test.

Table 3 Kaplan-Meier all-cause survival probabilities: patients with EC-LUSC, EC-LUAD, LUSC-1and LUAD-1

	LUSC		**LUAD**	
	EC-LUSC	LUSC-1	EC-LUAD	LUAD-1
Overall	139	108582	138	199867
6 months (SE)	72.6% (0.038)	73.4% (0.001)	81.0% (0.035)	75.5% (0.001)
1 year (SE)	47.8% (0.044)	54.1% (0.002)	66.3% (0.043)	59.2% (0.001)
2 year (SE)	27.8% (0.042)	35.1% (0.001)	47.2% (0.048)	42.6% (0.001)
3 year (SE)	19.2% (0.038)	27.0% (0.001)	33.0% (0.047)	33.9% (0.001)
5 year (SE)	13.8% (0.036)	19.2% (0.001)	25.7% (0.047)	24.7% (0.001)
10 year (SE)	Unknown	9.3% (0.001)	12.4% (0.049)	14.4% (0.001)
Median, months	11	13	22	17
P	0.023		0.681	
Localized	58	24702	56	44559
6 months (SE)	81.0% (0.051)	89.7% (0.002)	89.0% (0.042)	95.4% (0.001)
1 year (SE)	55.3% (0.067)	79.5% (0.003)	79.1% (0.056)	89.9% (0.001)
2 year (SE)	46.7% (0.069)	63.9% (0.003)	64.0% (0.069)	79.9% (0.002)
3 year (SE)	29.5% (0.068)	53.3% (0.003)	42.3% (0.075)	71.7% (0.002)
5 year (SE)	Unknown	40.0% (0.003)	31.6% (0.078)	58.8% (0.003)
10 year (SE)	Unknown	19.7% (0.003)	31.6% (0.078)	37.5% (0.003)
Median, months	20	40	30	81
P	<0.001		<0.001	
Regional	32	37851	32	46705
6 months (SE)	74.1% (0.079)	81.4% (0.002)	93.5% (0.044)	89.7% (0.001)
1 year (SE)	57.2% (0.090)	62.8% (0.003)	83.1% (0.069)	76.9% (0.002)
2 year (SE)	22.8% (0.082)	41.7% (0.003)	59.7% (0.096)	59.4% (0.002)
3 year (SE)	22.8% (0.082)	31.6% (0.003)	49.6% (0.103)	48.0% (0.002)
5 year (SE)	17.1% (0.079)	22.4% (0.002)	44.1% (0.105)	34.9% (0.002)

10 year (SE)	Unknown	9.7% (0.002)	9.2% (0.084)	19.4% (0.002)
Median, months	14	18	34	33
P	0.140		0.971	
Distant	42	42561	43	108603
6 months (SE)	62.7% (0.076)	57.1% (0.002)	60.8% (0.077)	61.3% (0.001)
1 year (SE)	29.0% (0.073)	32.1% (0.002)	35.9% (0.078)	39.0% (0.002)
2 year (SE)	7.7% (0.048)	14.1% (0.002)	13.7% (0.061)	20.0% (0.001)
3 year (SE)	3.9% (0.036)	8.5% (0.001)	6.8% (0.046)	12.2% (0.001)
5 year (SE)	Unknown	5.0% (0.001)	3.4% (0.033)	6.0% (0.001)
10 year (SE)	Unknown	2.0% (0.001)	unknown	2.4% (0.001)
Median, months	7	7	7	8
P	0.229		0.185	

Abbreviations: LUSC, lung squamous carcinoma; EC, esophagus cancer; EC-LUSC, secondary primary LUSC after EC; LUSC-1, first primary LUSC; LUAD, lung squamous carcinoma; EC-LUAD , secondary primary LUAD after EC; LUAD-1, first primary LUAD; SE, standard error.

Table 4 Multivariate Cox Regression Analysis evaluating the HR of a History of EC on OS for localized LUSC and localized LUAD.

	Localized LUSC		Localized LUAD	
	All Complete Cases	**Multiple Imputation for All Cases**	**All Complete Cases**	**Multiple Imputation for All Cases**
All (n)	19531	24760	36100	44615
HR (95% CI)	2.49 (1.75-3.54)	1.91 (1.41-2.59)	2.63 (1.71-4.03)	2.13 (1.48-3.05)
P	<0.001	<0.001	<0.001	<0.001
Omitting <one-year Latency (n)	19524	24750	36085	44594
HR (95% CI)	2.50 (1.69-3.70)	1.82 (1.29-2.56)	2.51 (1.43-4.43)	1.89 (1.20-2.99)
P	<0.001	<0.001	0.001	0.006
Omitting <two-year Latency (n)	19514	24735	36080	44587
HR (95% CI)	2.62 (1.71-4.02)	2.22 (1.51-3.27)	3.47 (1.92-6.28)	2.13 (1.30-3.48)
P	<0.001	<0.001	<0.001	0.003

Data were presented as HR (95% CI) and P values derived from Cox proportional hazards model adjusted for sex, race, age at LC diagnosis, year of LC diagnosis, grade of LC, and surgery for LC

Abbreviations: HR, hazard ratio; 95% CI, 95% confidence interval; EC, esophagus cancer; LC, lung cancer; OS, overall survival; LUSC, lung squamous carcinoma; LUAD, lung squamous carcinoma; 95% CI, 95% confidence interval.

Figures

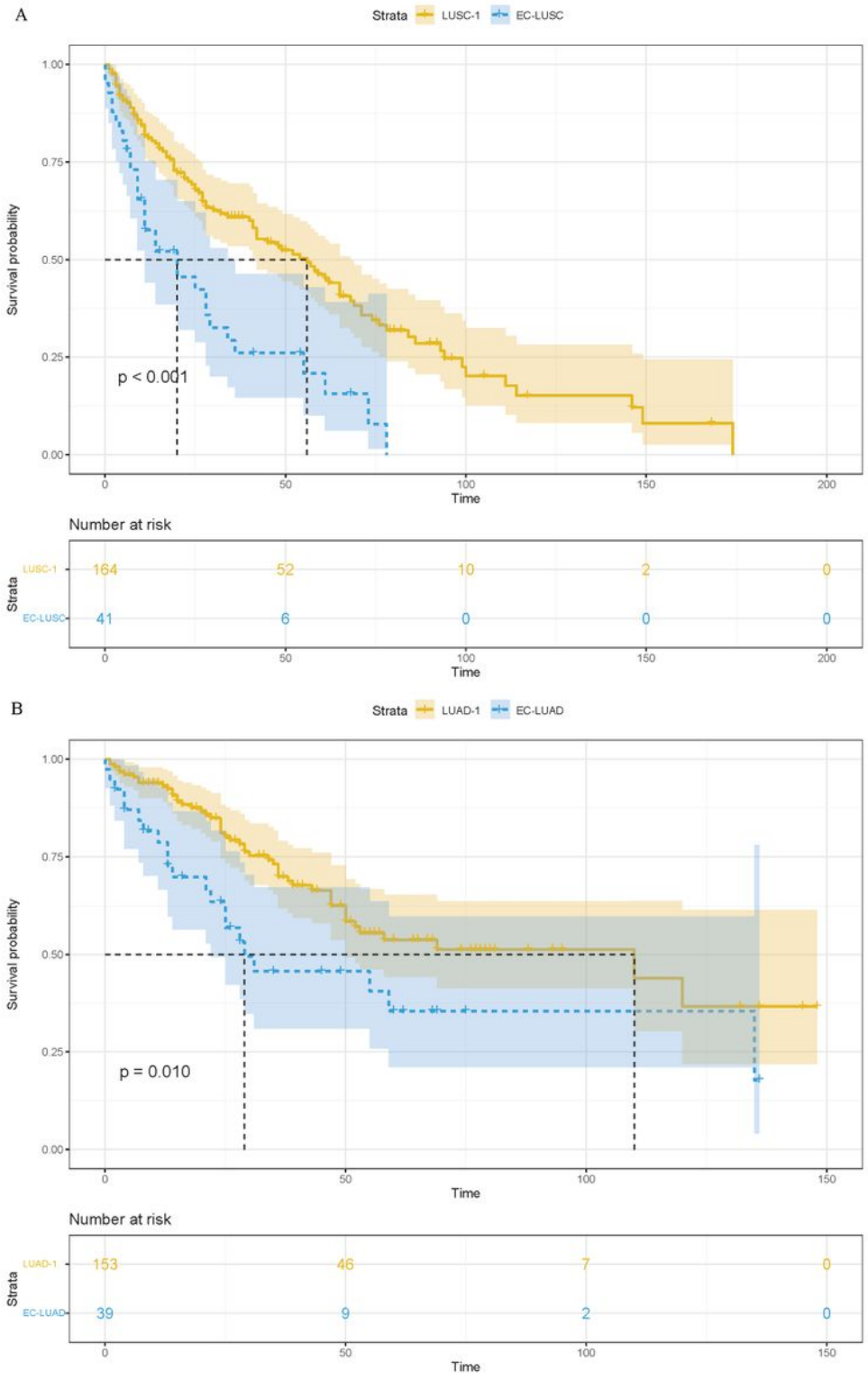

Figure 1

Kaplan-Meier Survival curves stratified by the history of EC for localized LUSC and localized LUAD after propensity score-matching analysis. A, localized LUSC; B, localized LUAD Abbreviations: EC, esophagus cancer; EC-LUSC, secondary primary LUSC after EC; LUSC-1, first primary LUSC; LUAD, lung squamous carcinoma; EC-LUAD , secondary primary LUAD after EC; LUAD-1, first primary LUAD.

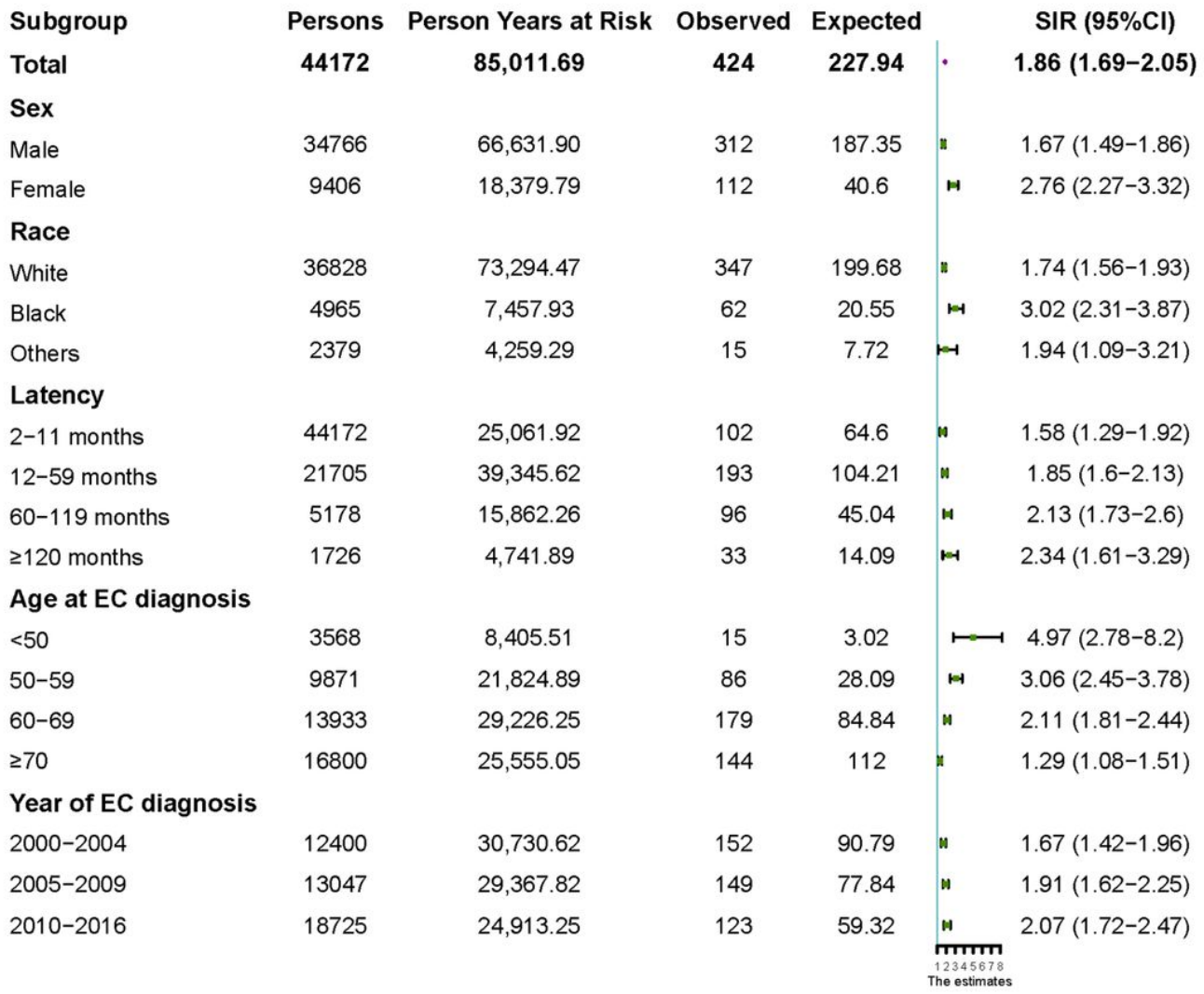

Figure 2

Forest plot summarizing risk for SPLC among patients with EC according to patient and treatment. The risk of developing SPLC was statistically significantly elevated in all subgroups (P < 0.05). Abbreviations: SPLC, secondary primary lung cancer; EC, esophagus cancer.

Supplementary Files

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